



DATE: JUN 28 2011

FROM: Helen Chen, M.D., Investigational Drug Branch, CTEP, DCTD, NCI

SUBJECT: Bevacizumab (rhuMAb VEGF) NCI IND Safety Report, AE# 16456507

TO: Investigators Using Bevacizumab (NSC 704865)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent bevacizumab.

The following must be completed by all investigators using bevacizumab under NCI INDs 7921 and 11460.

- Send a copy of this letter to your Institutional Review Board (IRB) of record according to your policies and procedures.
- File a copy of this letter in your protocol file.

If your study is not covered under INDs 7921 or 11460 it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with bevacizumab, there does not appear to be a change in the risk-benefit ratio for bevacizumab studies; therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSC, and the total number of patients enrolled in trials under these INDs and/or NSC.

A 66-year-old female with invasive breast cancer developed grade 4 respiratory failure, grade 4 hypotension, urinary tract infection and then expired while on a phase 3 study utilizing the investigational agent bevacizumab in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim.

ADVERSE EVENTS ASSESSMENT

IND 7921 NSC 704865 Bevacizumab (rhuMAb VEGF)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: # 1 Event: Gr. 5: Death NOS Gr. 4: Respiratory failure Gr. 4: Hypotension Gr. 4: Infection (urinary tract)
AE: 1645650	Protocol: E5103

The patient was a 66-year-old female with invasive breast cancer who developed hypotension, respiratory failure, and urinary tract infection and then expired while on a phase 3 study utilizing the investigational agent bevacizumab/placebo in combination with doxorubicin, cyclophosphamide, paclitaxel, and pegfilgrastim. She began her first course of treatment on February 4, 2010, receiving bevacizumab 10 mg/kg IV over 30-90 minutes on Day 1, doxorubicin 60 mg/m² IVP on Day 1, cyclophosphamide 600 mg/m² IV over 20-30 minutes on Day 1, and pegfilgrastim 6 mg SQ on Day 2, every 14 days during Cycles 1-4. She then received bevacizumab 15 mg/kg IV over 30-90 minutes on Day 1 and paclitaxel 80 mg/m² IV over 1 hour on Days 1, 8, and 15, every 21 days during Cycles 5-8. She received her last dose of bevacizumab on June 17, 2010 (Cycle 8, Day 1), her last doses of doxorubicin and cyclophosphamide on March 25, 2010 (Cycle 4, Day 1), her last dose of pegfilgrastim on March 26, 2010 (Cycle 4, Day 2), and her last dose of paclitaxel on June 24, 2010 (Cycle 8, Day 8). The treatment coded was unblinded and the patient had received bevacizumab and not the placebo.

The patient was diagnosed with invasive breast carcinoma in November 2009. She was status post right modified radical mastectomy in November 2009. The patient began the investigational therapy on February 4, 2010. The patient's past medical history was significant for type 2 diabetes, morbid obesity, and obstructive sleep apnea requiring CPAP at night. Her baseline echocardiogram showed normal left ventricular function with a left ventricular ejection fraction (LVEF) of 65%.

When presenting for Cycle 3 of therapy on March 4, 2010, the patient complained of dyspnea which was worse than her baseline. Her blood pressure (BP) was 152/94 mmHg, and her oxygen saturation was 93% on room air. She was sent to the ER for the dyspnea and given Lasix[®] which led to improvement. A CT scan on March 11, 2010 was negative for pulmonary embolus (PE). She received the cycle 3 and cycle 4 of the study therapy.

The patient continued to have moderate fatigue and dyspnea on exertion. A March 31, 2010 (prior to cycle 5), echocardiogram revealed an LVEF of 65%, a diastolic filling pattern suggestive of impaired relaxation, and mild mitral regurgitation. She was hospitalized for febrile neutropenia with a urinary tract infection at the end of cycle 4. She had experienced a 25 pound weight loss (to 281 pounds), peripheral neuropathy of both hands and feet. The study therapy was continued. On a clinical visit on June 10, 2010, her main complaint was fatigue and reported spending most of time in a recliner. Cardiac and lung exams were unremarkable. She had lower extremity edema which did not change significantly from baseline. Although her dyspnea was unchanged, she experienced 2 episodes of palpitations lasting less than 1 minute.

On June 23, 2010 (Cycle 8, Day 7), the patient presented to the clinic for evaluation prior to receiving her scheduled paclitaxel the next day. The patient complained of marked weakness, so much so that she was unable to lift her left leg onto the bed forcing her to sleep on the floor. She still had chronic lower extremity edema, and her dyspnea was unchanged. Her WBC that day was 4.5 K/ μ L (reference range: 4.8-11.0 k/ μ L) with a normal ANC; her hemoglobin was 9.6 g/dL (reference range: 12.0-16.0 g/dL) and hematocrit 28.3 % (reference range: 37.0-47.0 %) with normal platelets. The following day, the patient

presented to the clinic to receive the investigational treatment. Her vital signs were stable upon arrival, and the paclitaxel was infused without incident. After the infusion, however, the patient became lethargic, pale, hypotensive with a blood pressure (BP) of 58/40 mmHg, and hypoxic with an oxygen saturation of 89-90%. The patient was started on IV fluids and oxygen, which improved her responsiveness and increased her oxygen saturation to 95%. When EMS arrived, the patient was still hypotensive (52/38 mmHg), and her blood glucose was 258 mg/dL. She was taken to the emergency room, where her BP was 87/43 mmHg; it was noted that the patient was not in acute distress. The patient's urinalysis was indicative of a urinary tract infection. A V/Q scan revealed low probability for PE. A suboptimal echocardiogram revealed normal LV thickness and size, decreased LV systolic function (precise reading was not given) and trivial pericardial effusion. She was started on a dopamine, Maxipime[®], and vancomycin. The patient was admitted to the ICU, and started on Levophed[®] and Lovenox[®]. She was initially placed on BiPAP, but was later intubated and placed on mechanical ventilation. The patient was also started on Cubicin[®], meropenem, and micafungin. Laboratory abnormalities from June 24 to June 25, 2010, included a myoglobin of 41.5 ng/mL (reference range: 14.3-65.8 ng/mL) which worsened to 3716.9 ng/mL, and a BNP of 309 pg/mL (reference range: <100 pg/mL). She had a creatinine of 2.79 mg/dL (reference range: 0.42-1.06 mg/dL) and a potassium of 7.4 mmol/L (reference range: 3.5-5.1 mmol/L), for which she underwent transient hemodialysis.

On June 26, 2010 (Cycle 8, Day 10), the patient developed a fever with a maximum temperature of 101°F, and was placed on Levaquin[®] and Zovirax[®]. Her ANC was 750 cells/mm³ (reference range: ≥ 1500 cells/mm³), and she was started on Neupogen[®]. A chest X-ray that day showed generalized cardiomegaly with pulmonary venous congestion. At that time, it was felt that the patient had acute renal insufficient with underlying acute tubular necrosis and systemic inflammatory response syndrome/acute respiratory failure all in the setting of sepsis/septic shock. On June 27, 2010 (Cycle 8, Day 11), the patient's urine culture drawn on June 24, 2010, was positive for multidrug resistant strain *Klebsiella oxytoca*; blood cultures were negative. She was started on IV Tygacil[®] and Primaxin[®]. The patient's BP improved to 118/70 mmHg, and the tapering off Levophed[®] was considered. There was no documentation of a CT scan of the chest on the patient.

On June 29, 2010 (Cycle 8, Day 13), the patient's BP was 135/85 mmHg, and she was taken off vasopressors. She was started on Total Parenteral Nutrition (TPN). During the next several days, the patient remained intubated on mechanical ventilation, and unresponsive without sedation. The patient later became hypotensive, and afterwards went into atrial fibrillation. She was started on IV fluids and amiodarone.

On July 12, 2010 (Cycle 8, Day 26), the patient was extubated, but later had to be reintubated. A July 16, 2010, echocardiogram revealed normal LV thickness and size, preserved LV systolic function with an estimated EF of >60%, mild septal hypokinesis, and a small pericardial effusion. She was later extubated on July 23, 2010. On July 26, 2010, the patient became hypotensive, tachycardic, and tachypneic. A chest X-ray showed a worsening of pulmonary venous congestion and development of minimal interstitial edema as compared to that of July 23, 2010. She was restarted on dopamine and Levophed[®], and placed on a BiPAP. On July 27, 2010, the patient was transferred to a rehabilitative hospital, where she again had to be emergently intubated, and continued on antibiotics. On July 28, 2010, the patient went into ventricular tachycardia/ventricular fibrillation. An echocardiogram revealed small pericardial effusion and an ejection fraction of 70%. Resuscitative measures were unsuccessful, and she expired that day.

The patient's past medical and surgical history was significant for type 2 diabetes, hypertension, hyperlipidemia, morbid obesity, obstructive sleep apnea on CPAP, resolved acute renal failure, and supraventricular tachycardia. She also had history of flesh eating disease of the left lower extremity 12 years ago, left leg cellulitis, osteoarthritis, and surgical history included hysterectomy, appendectomy in 1952, 2 caesarian sections in 1975 and 1979, dilatation and curettage, and skin grafting in 1998.

Medications taken at the time of the event were potassium chloride, Enblex[®], clonidine, Toprol[®], stool softener, Questran[®], Ambien[®], simvastatin, Micardis[®], Rythmol[®], Lyrica[®], Voltaren[®], Lasix[®], Amaryl[®], Tekturna[®], Tarka[®], insulin, and Compazine[®].

There have been 167 other cases of death NOS, 57 cases of sudden death, and 30 other cases of respiratory failure reported to NCI as serious adverse events through AdEERS under the bevacizumab NSC and/or IND.

Adverse Event	Grade	Attribution
Death NOS (n=167)	5	62 Unrelated, 70 Unlikely, 34 Possible, 1 Probable
Sudden death (n=57)	5	6 Unrelated, 11 Unlikely, 37 Possible, 3 Probable
Respiratory failure (n=30)	5	2 Unrelated, 6 Unlikely, 9 Possible
	4	4 Unrelated, 3 Unlikely, 3 Possible
	3	1 Unrelated, 2 Unlikely


There have been 33,125 patients enrolled in NCI-sponsored clinical trials under the bevacizumab IND and/or NSC.

In this case, the cause of death may be multi-factorial and included infection, cardiac dysfunction and comorbidities. A possible relationship to the protocol therapy (including chemotherapy and bevacizumab) cannot be excluded.

	Death NOS	Respiratory failure	Hypotension	Infection (urinary)
Bevacizumab	Possible	Possible	Possible	Possible
Doxorubicin	Unrelated	Unrelated	Unrelated	Unrelated
Cyclophosphamide	Unrelated	Unrelated	Unrelated	Unrelated
Pegfilgrastim	Unrelated	Unrelated	Unrelated	Unrelated
Paclitaxel	Probable	Possible	Possible	Possible
Invasive Breast Cancer	Unrelated	Unrelated	Unrelated	Unrelated
Urinary tract infection	Unlikely	Unlikely	Possible	Possible
Possible diastolic dysfunction	Possible	Possible	Unlikely	Unlikely

Date: 6/30/11

Signature:


 Helen Chen, M.D.
 (IDB Monitor for bevacizumab)

If this assessment is changed, we will notify your office.

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